American Journal of Pharmacy

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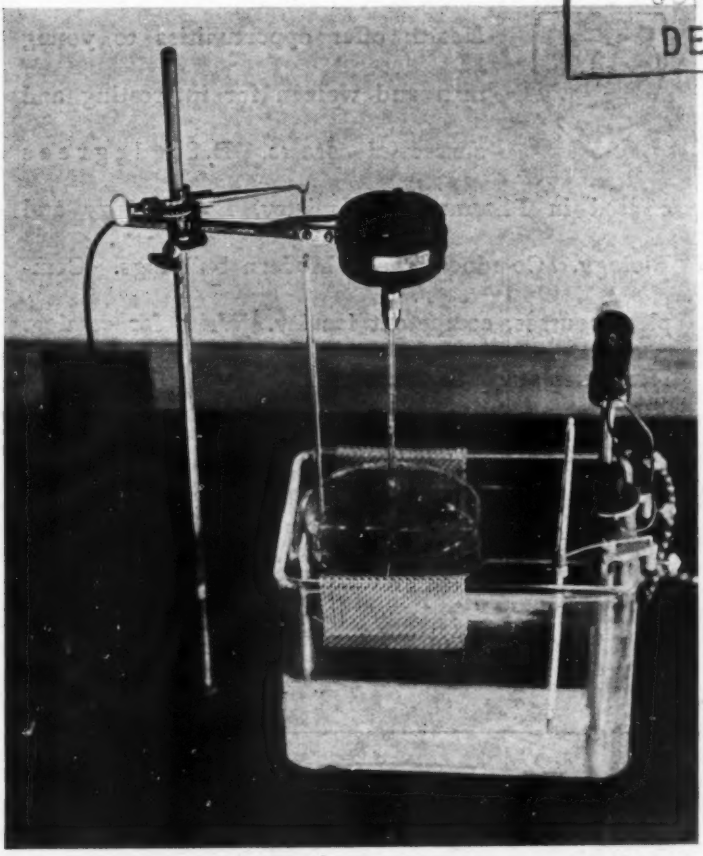

APPARATUS USED IN TESTING TABLETS FOR RATE OF DISINTEGRATION

(See article on Control of Tablets, p. 124)

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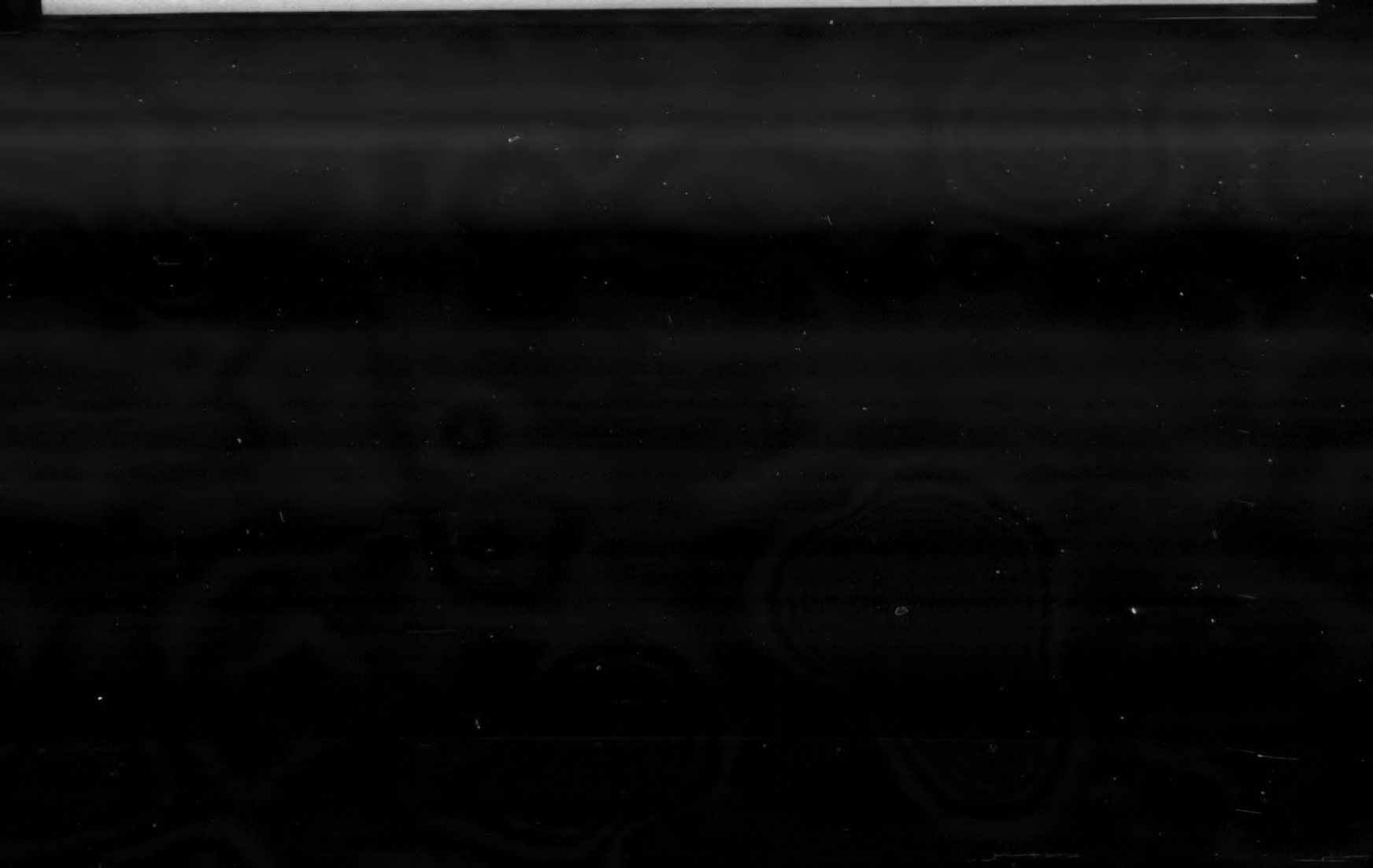

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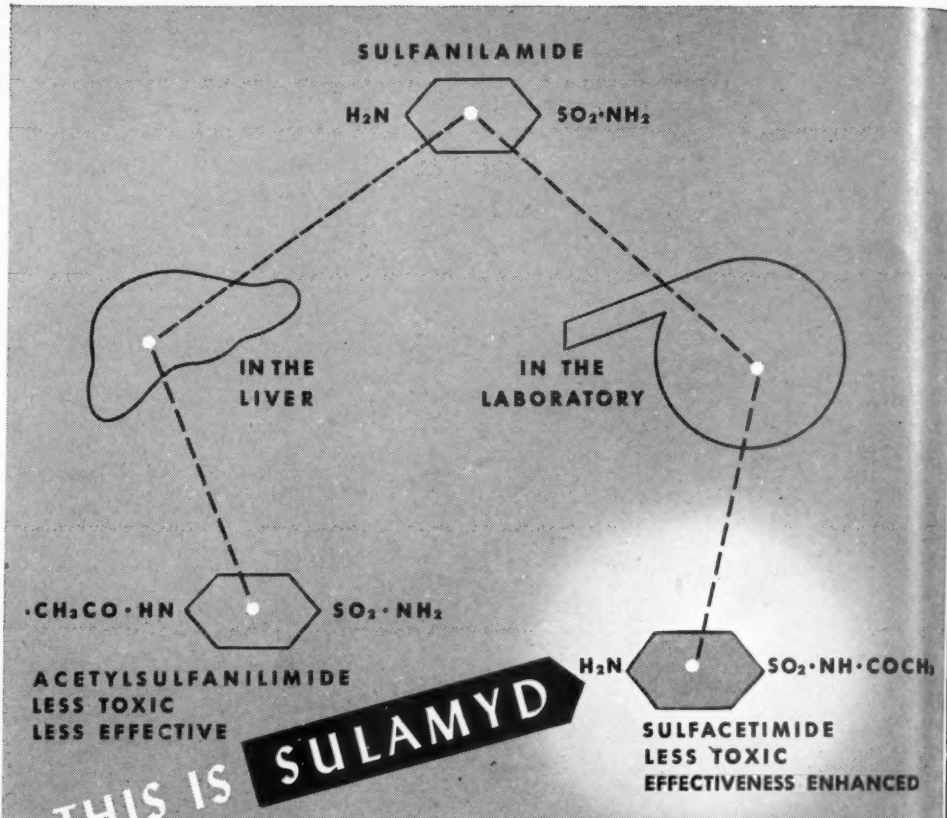

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Am. J. Psychiat., July, 1922.

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AMERICAN JOURNAL OF PHARMACY

AND THE SCIENCES SUPPORTING PUBLIC HEALTH

Since 1825

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E D I T O R I A L

PHARMACOPŒIA OR GOVERNMENT

A RECENT publicity release sent out by one of our large pharmaceutical manufacturers has given us sufficient concern to prompt this editorial. The release called attention to some present difficulties with the official standards for ampuls as determined by a survey made for the Contact Committee of the American Drug Manufacturers' Association. The particular point in question is the appearance of injection medication from the standpoint of undissolved material wherein the Pharmacopœia requires them to be ". . . clear, and free of any turbidity or undissolved material which can be detected readily without magnification when the solution is examined against black and white backgrounds with a bright light reflected from a 100-watt Mazda lamp or its equivalent."

The release claimed a number of things, for example, that 15-20 per cent of all parenteral solutions are rejected by industry for failure to comply with this standard although with individual plants rejections range from one-half of one per cent in one to 50 per cent in another.

It is, however, the latter part of the release to which we object. It is as follows: "The report notes that, while U. S. P. is supposed to be the standard-making agency, manufacturers have gone to the F. D. A. to have them set the real standard. 'In other words,' it says, 'here is a case in which the F. D. A. has taken up where the U. S. P. and N. F. have left off and provided standards in an effort to be helpful. If there can be said to be a standard it is certainly the F. D. A. standard and not the U. S. P. or the N. F. provision'."

Our objections to this release are numerous. In the first place if this is the opinion of the committee assigned to investigate this problem it is at least in poor taste to circulate such statements through the medium of an advertising agency. Can it be that such dramatic statements are made intentionally for purely purposes of propaganda? The heretofore close cooperation of industry, pharmacopœia and government does not seem to warrant such a stinging reprimand to a group that has conscientiously tried to perform its work in a fair and open-minded manner.

From the purely technical standpoint is the F. D. A. setting the standard for the appearance of solutions? We think not. It is simply interpreting the term "detected readily" in a liberal manner and

exercising administrative judgment which is its duty and privilege under the law. The Pharmacopœial standard is still being used by the F. D. A., which, after all, *is required by law.*

It is with honest chagrin that we envision the continued but subtle efforts by many individuals in the drug field to have the F. D. A. become the standard-setting agency in the field of medicinals. Thus for no really defensible reason we see that penicillin standards are to be set by the F. D. A. Not so much because the F. D. A. seeks greater power but because American medicine and pharmacy have permitted it to happen by default!

Let us be honest with ourselves. Is the public welfare likely to be better protected under a system whereby one government agency decides what drugs may or may not be used, what the standards shall be, and also enforces its own standards? Should so much power reside in one group without any checks or balances except those provided by political pressure? We think not.

The United States Pharmacopœia is not in any sense specially favored by this writer and it has frequently felt the sting of his critical pen. But basically it is a democratically conceived body representing each group in the broad field of medicine in the United States. It is open to comment and suggestion by all and its policy on standards is dictated by a majority vote of its fifty members of the Revision Committee. If changes are needed in Pharmacopœial standards there are immediate and direct avenues of approach whereby this can be accomplished by any responsible group.

The drug industry in the United States would do well to be less destructive in its public criticism of this organization so necessary to free enterprise in its field. The Pharmacopœia cannot afford the luxury of a publicity agent to counteract such critics. Granted it is an imperfect organization but what one isn't? Is the record of any manufacturer or even government without a blemish? Can we be sure that a marriage of government and industry would be a condition of perpetual harmony? We must remember that fascism was but an unholy alliance between government and industry, prospering industry for but a time, when it was then devoured by its partner. Historic events give ample evidence of this truth. Let us work and strive for a continued democracy in the standardization of drugs, criticizing when criticism is due but in the proper manner and spirit.

L. F. Tice.

THE PHYSICAL CONTROL AND STANDARDIZATION OF COMPRESSED AND COATED TABLETS

By Fred J. Bandelin *

LITTLE has been published in pharmaceutical literature on the various phases of tablet manufacture and least of all on physical control and standardization. These important phases of tablet production are left largely to the good faith and discretion of the manufacturer. Although raw materials are controlled by specifications of the official and other compendia, no specifications or standards are available for the finished tablets. Certain methods and procedures must therefore be adopted by the manufacturer to assure uniformity in concentration of ingredients, and in size, shape, color, hardness, coating and disintegration. Procedures must be set up to carry out and maintain this standardization. Adequate and good control depends, of course, on the specifications set up by the control department and results from the desire to produce uniform tablets of exact dosage and superior quality. Although physical control is as important as chemical control, it may never take the place of it. Both must be exerted and adequate physical control will invariably produce more uniform findings in chemical analysis. Such control becomes of prime importance in the manufacture of tablets containing minute amounts of potent medicaments such as alkaloids or hormones.

The systematic control of compressed tablets includes not only methods of testing but also the recording and filing of the results of tests performed so that these are readily available on a standard form adopted for the purpose. Such a system of records will show, over a period of time, what variation may be expected from batch to batch of any single formula.

Tablet specifications on the master formula should denote, along with the list of ingredients and process for manufacture, the form of the tablet, that is, the weight, shape, size, type of face and coating.

Since the shape of tablets is limited only by the restrictions of die making, many manufacturers prefer distinctive shapes and colors to identify their products. Care must be exercised to use the same type of punches and dies from batch to batch in order to assure con-

* From the laboratories of Flint, Eaton & Company, Decatur, Illinois.

stant uniformity. The size, type and shape of the punch surface should be adequately described in the specifications on the master formula.

It is essential that tablets for analysis be taken by the control chemist in order to assure proper and uniform sampling. Samples for checking weight, dimensions, hardness and color should be taken as soon as all adjustments have been made on the compressing machine and before the batch is compressed. If any error or serious deviation from the specifications is found at this point, it will prevent compressing and then reworking the entire batch. This will be necesary if the tablet does not meet the specifications after the entire batch is completed. For this reason, samples should be taken after all adjustments are completed and the machine has been running at full speed for several minutes. If this sample is found to meet the specifications, the batch is compressed. If the sample does not meet the specifications, the control chemist gives instructions for further adjustments. When the entire granulation has been compressed, samples must again be taken to assure that no serious changes have occurred. A sample from the completed batch is filed for further reference.

The testing of tablets to be controlled consists of examination for appearance, color, form, weight, resistance to breakage, water content, disintegration in water or in digestive fluids, and, in the case of enteric coatings, digestibility.

The scope of this paper includes not only compressed tablets but also enteric-coated and sugar-coated tablets since these require much the same control as uncoated tablets plus control of the coating. Uncoated tablets will be considered first and coated tablets separately in the latter part of the paper.

Appearance of Tablets

All tablets of the same batch and tablets of various batches of the same formula should be uniform in appearance. The faces should be smooth and uniform in color. Tablets whose edges differ in color from the faces indicate lack of sufficient lubrication. Shoulders of the tablet should be clean cut. Ridges about the perimeter extending above the faces of the tablet are caused by too much clearance between punches and dies resulting from excessive wear.

Tablets are best examined with a hand magnifying glass in order to aid in finding defects. White tablets should be uniformly white

and not mottled or gray or have visible specks of foreign material. Colored tablets likewise should be uniform in color. Mottled tablets indicate insufficient mixing and poor distribution either of the ingredients or of the dye, or both. Very small particles of colored material, otherwise not discernible by the eye, are spread out, when subjected to the pressure of compressing, to form a noticeable spot on the tablet face. Also, concentrations of hygroscopic material, resulting from insufficient mixing, absorb moisture with a resulting change of color.

Shape

Tablets having the conventional round shape should be checked for diameter measurement using a caliper graduated in 1/32 inch (Fig. 1). Since the diameter is determined by the punches and dies

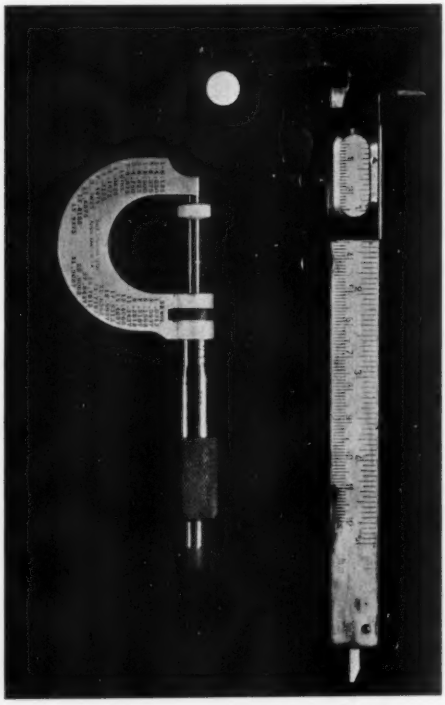

FIGURE 1

used, this dimension is fixed and increases in 1/32 inch increments for all standard punches and dies. This measurement will vary only slightly even with excessive wear of dies. The control chemist merely checks the diameter of the tablet to assure that the proper size punches and dies have been used in compressing.

Conventionally round tablets have more or less convex faces. The degree of curvature of this surface is determined by the type of punches used. These are generally designated as regular, deep cup and triple deep cup. Tablets of various other shapes such as elliptical, square, triangular, etc., may also be measured for size with the caliper. These tablets may be regarded as having three dimensions, while the round tablets have but two: diameter and thickness.

The thickness of tablets is best measured with a 0-1 inch screw micrometer with a ratchet attachment (also Fig. 1). The tablet is placed between the open measuring surfaces of the micrometer and these are slowly brought to bear upon the faces of the tablet by means of the screw until the sound of the ratchet indicates that there is no more clearance. The thickness is then read and recorded in thousandths of an inch.

The thickness of round tablets with convex faces is measured at the center of the tablet which is the thickest part. This holds true for all tablets having convex faces regardless of shape. In determining the thickness of tablets with flat faces this is, of course, obviated since the thickness measurement may be taken at any point on the parallel faces.

Some tolerance is permitted in tablet thickness to take care of any adjustment necessary, within limits, to produce a tablet of proper weight and hardness. Tolerance on the usual 5-grain tablet is about 0.01 inch either way from the standard. Tolerances are relative to the size of the tablet and may be greater for larger tablets.

An excellent method to check the shape and size of odd shaped tablets is to have a scale drawing of the tablet on the master formula upon which the tablet may be laid for comparison.

The shape and dimensions of the tablet should not vary from batch to batch with the possible exception of some small deviation in thickness to overcome slight discrepancies in manufacture and to produce tablets of uniform hardness.

Tablet Weight

The weight of the tablet is usually determined by taking an average of at least twenty tablets. A large representative sample should be obtained by taking tablets from various parts of the batch. The samples are then mixed and twenty of the tablets are weighed to obtain an overall average of the batch. Hörst-Madsen (1) suggests that thirty tablets be taken for average weight so that the limits are not too close. The control chemist may supplement these determinations by having a trained worker in the tablet compressing department take a sample of tablets as they come from the machine at regular intervals, say every thirty minutes or every hour, and weigh them to find the average. These weighings may be recorded with the time taken to give a running average throughout the batch.

Many control departments establish a flat 3 per cent tolerance range as a maximum variation for the average weight. The 7th Addendum of the British Pharmacopœia directs that the average tablet weight be determined by weighing twenty tablets. When weighed singly, not more than two of the tablets deviate from the average weight by a greater percentage than that shown in the following table, and no tablet deviates by more than double that percentage. If twenty tablets are not available, ten may be used for the determination; not more than one then deviates from the average weight by a greater percentage than shown in the table, and no tablet deviates by more than double that percentage.

TABLE 1

Average weight	Percentage deviation
2 grains or less	± 10 %
More than 2 grains and less than 5 grains	± 7.5%
5 grains or more	± 5 %

The Addendum further gives limits of standards for the average weight of drug in tablets to allow for variations due to manufacturing processes, for variations in standards of purity of pharmacopœial drugs and for any other permissible cause. These limits are based on the requirement that twenty tablets are used for assay. In circumstances where twenty tablets cannot be obtained, a smaller number, which may not be less than five, may be used, but in order to allow

for sampling errors, the limits of the standards are widened in accordance with the following table.

TABLE 2

To apply when the stated limits are between 90 and 110 per cent.

Weight of drug in each tablet	Subtract from the lower limits for samples of			Add to the upper limits for samples of		
	15	10	5	15	10	5
Less than 2 grains	0.2	0.7	1.6	0.3	0.8	1.8
2 grains and less than 5 grains	0.2	0.5	1.2	0.3	0.6	1.5
5 grains or more	0.1	0.2	0.8	0.2	0.4	1.0

For limits less than 90 or greater than 110 per cent proportionally smaller or larger allowances should be made.

If more elaborate control is desired, a number of tablets (50 to 100), properly sampled from a batch, should be weighed individually and the standard deviation from the arithmetic mean determined by the formula.

$$\text{S.D.} = \sqrt{\frac{\Sigma d^2}{n}}$$

where Σd^2 is the sum of the deviations squared and n is the number of determinations. A maximum standard deviation also may be adopted as a weight control.

Beeler (2) has also offered procedures for the calculation of maximum and minimum per cent variation in tablets.

Moisture Content

The moisture content of tablets or tablet granulations may be an important factor in their stability and keeping qualities. In many cases where these are not impaired, moisture may cause discoloration which, in time, detracts from the appearance of the tablet. Ascorbic Acid tablets, for instance, have a tendency to turn dark and develop an odor similar to burnt sugar if the water content of the granulation is not kept below 3.5 per cent. Moisture content is especially impor-

tant in tablets intended for coating because of its detrimental effect on coatings. The prime requisite for good coatings is a dry tablet. In all cases, therefore, where moisture content is important, it should be determined on the granulation immediately before compressing.

To accomplish this, grind the granulation to a fine powder, take a weighed sample and dry at 110° C. for two hours, cool in a desiccator, and calculate the moisture by difference. In cases where this temperature affects the constituents or causes loss of weight by decomposition, the powdered aliquot may be dried in a vacuum desiccator over phosphorus pentoxide for twenty-four hours. An alternate method in granulations or coated tablets, where it is suspected that the water content is high, is the U. S. P. XII toluene extraction method using the Bidwell and Sterling moisture determination apparatus.

Disintegration of Tablets

Methods for determining the disintegration of tablets fall into two classes: (1) those which attempt to measure the mechanical resistance of tablets to various types of shock and strain, and (2) those which test the speed with which tablets break up when placed in a specified liquid under certain conditions. The methods which come under the first classification are usually referred to as "hardness testing" and attempt to predict the relative disintegration of tablets.

A great many manufacturers mistakenly believe that well made hard tablets do not disintegrate and are therefore tempted to make their tablets too soft. This may be an excellent sales point but it is not necessarily true in practice, since the hardness or softness of tablets is not the sole index of their ability to disintegrate. This ability to disintegrate is largely dependent upon the formula and much may be accomplished toward this end by manipulating and balancing the formula and by including various dispersing agents.

There is no doubt that excess pressure in compressing may interfere with disintegration and therefore hardness should be judiciously controlled. Tablets should be hard enough to resist ordinary shock in handling, packaging and shipping, yet not so hard as to be objectionable. Davis and Gillette (3) have stated that a tablet should be capable of resisting a fall of several feet onto a hard surface, and on storage, little or no powder should accumulate in the container.

Undoubtedly some hardness methods are of value in predicting the disintegration of tablets. A number of these methods have been described. Brown (4) advocates a method which attempts to determine the mechanical resistance and disintegration in absolute values. This method employs a balance-like device to determine the amount of weight required to break the dry tablet and the tablet immersed in water or artificial gastric fluid. There is also available a hardness testing device* (Fig. 2) which measures the resistance of the tablet

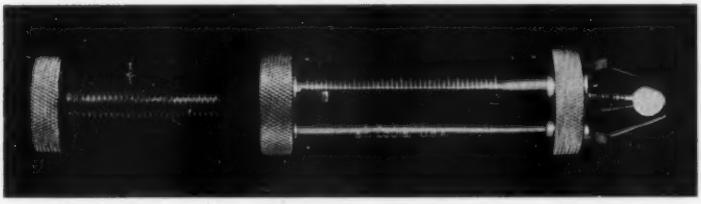

FIGURE 2

to pressure. It consists of a spring equipped with a screw to tighten down a hammer against the tablet held in a stirrup. An indicator on the spring moves along a scale which is calibrated in kilograms. This shows the pressure required to break the tablet. Miller and Shalkova (5) have described a small crushing press and the derivation of a formula for estimating the strength or hardness of tablets.

Among the Type 2 methods are a number of simple procedures which consist of immersing the tablet, with or without agitation, in water or various digestion fluids. Malpass (6) suggests that the tablets be suspended in gastric juice and states that they should then disintegrate in thirty minutes. The Swiss Pharmacopœia,(7) which is the first Pharmacopœia to include a test and specifications for tablet disintegration, directs that the tablet be placed in a 100 cc. Erlenmeyer flask, that 50 cc. of water at 37° C. be poured upon it, and the flask shaken from time to time. After a maximum of 15 minutes, the tablet must be completely disintegrated or dissolved. Another method is suggested by the American Pharmaceutical Manufacturers Association.(8) This method uses a vertical glass tube with wire mesh covering the lower end. This is immersed in an

* Monsanto Chemical Co., St. Louis, Missouri.

artificial gastric fluid at 37° C. The tablet is dropped onto the wire mesh. Then a hog bristle brush is lowered into the tube until it touches the tablet; then raised. This is repeated at regular intervals until the tablet is disintegrated. Calamari and Roth (9) have reported on a testing device similar to the above with the exception that agitation is produced by bubbling air through the liquid. This causes a pulsation of the liquid up and down in the tube containing the tablets. The 7th Addendum to the British Pharmacopœia will include the following test for tablet disintegration. "Five tablets are used for the test. Place each tablet in a test tube 6 inches in length and 1 inch internal diameter, provided with a stopper and containing sufficient water, heated to 37° C., to fill the tube to within ½ inch of the stopper. Insert the stopper, place the tube in a water bath, maintained at 37° C., and repeatedly invert it at such a speed that the tablet travels through the water without striking the stopper or the bottom of the tube; the time required for the tablet to dissolve or disintegrate completely, unless otherwise stated in the monograph, is not more than 15 minutes. All five tablets should comply with the test. If one tablet fails to comply, the test should be repeated, using five tablets from the same sample; all must comply with the test."

These are by no means all of the methods available but are typical of the types of control methods in use.

For hardness testing we have found the spring instrument mentioned above to be rapid and easily used and to give fairly reproducible results in determining the dry breaking weight or mechanical resistance of the tablets to stress.

For disintegration in liquid we have used a method which is a modification of several of the above methods. This has proved reliable when considered in the light of reproducible results and has been serviceable and time-saving for routine control of tablet disintegration. This method is as follows. A circular piece of number 8 monel metal or stainless steel wire screen is suspended about 1½ inches below the top of a glass crystallizing dish, six inches in diameter. A glass stirrer attached to a slow speed or variable speed motor passes through a hole in the center of the screen so that the blade can turn clear of the dish and the screen. The crystallizing dish is filled with enough artificial gastric fluid to cover the tablets on the screen. The wire screen thus becomes a shelf just below the surface of the liquid to support the tablets. The temperature of the digestive fluid is

maintained at 37° C. by placing in a constant temperature bath. (Fig. 3.)

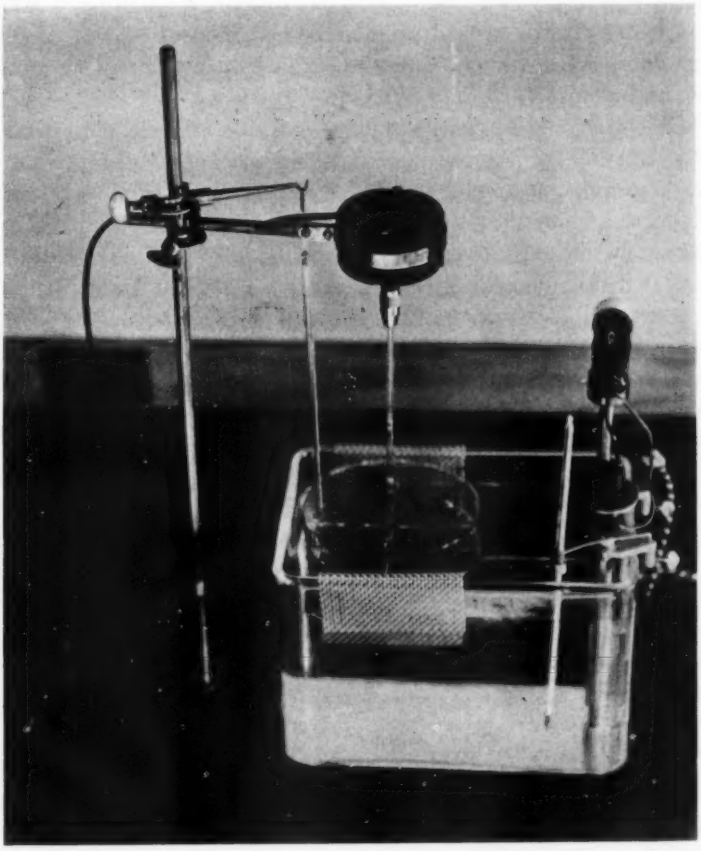

FIGURE 3

Ten to twenty tablets from a sample are placed on the screen and covered with gastric fluid at 37° C. and agitated slowly at a low, constant rate of speed. Tablets should disintegrate within thirty minutes. Using glass rod dividers, the wire screen may be divided so that a number of samples may be run at one time.

Coated Tablets

The control of tablet coatings is difficult and important. The human factor plays a great role in coating procedures making them difficult to standardize. Some standardization is possible, however, and this does much toward producing uniform and elegant coatings. The various subcoatings should be applied by measured amounts of liquid and weighed amounts of dusting powders. The average weight of the tablet should be checked often for this is an excellent indication of the amount of coating applied. Specifications should list the average weights of the tablets at the completion of various subcoatings and the weight of the finished tablets. The colored syrup used for finishing the coated tablets should contain a definite concentration of dye so that on application the specified weight and color of the tablet will be reached simultaneously. Although this is not always possible, tablets coated by this procedure will not vary too much in weight or color and can be adjusted to the proper shade and size without serious deviation from the standard.

Measurements of sugar-coated tablets may be taken with the screw micrometer and recorded in thousandths of an inch. Average weight may be determined as described under "Tablet Weight" in this paper. Color may be controlled by matching with a corresponding shade in the "Dictionary of Color" (10) or by preserving a satisfactory sample from a previous batch in a dark place to prevent fading. This may be used as a reference for all subsequent batches. Disintegration may be determined by one of the Type 2 methods previously described under "Disintegration of Tablets."

Enteric Coated Tablets

Many methods have been developed for determining the disintegration time of enteric coated tablets. Some of the outstanding methods are described here. Many others are merely modifications of these.

An early method of testing enteric coating was developed by Toplis (11) in 1915. This consisted of applying enteric coatings to an individual dose of Ipecac. The delayed action of the Ipecac was taken as a measure of the coating efficiency. In 1938 Husa and Magid (12) prepared enteric coated tablets of calcium sulfide and methylene blue. The effectiveness of the coating was determined as

follows: If the capsule dissolved in the stomach, regurgitation of hydrogen sulfide followed. If disintegration occurred in the intestine, the urine was colored blue and there was no regurgitation. Wruble (13) reported the use of a mechanical device using artificial gastric and intestinal fluids to test the solubility of the coatings. Mozsonyi (14) also suggested a method using artificial digestion fluid. Maney and Kuever (15) have also reported the use of a mechanical device for agitating tablets with artificial digestion fluids in small tubes immersed in a constant temperature bath. This device has a disadvantage in that the insoluble material washed off the tablets tends to cloud the fluid in the tubes, making it difficult or impossible to determine when the coating is dissolved. These investigators used artificial gastric fluid prepared by the formula proposed by Toplis (11) and acid, neutral and alkaline artificial intestinal fluids. Abbott and Allport (16) have described an apparatus in which the tablets are surrounded by artificial digestive fluids at 37° C. and are agitated by a current of air.

Bukey and Rhodes,(17) Bukey and Brew,(18) Worten et al.,(19) Goorley and Lee,(20) and Wruble (21) tested enteric coated tablets in vivo by radiographic examination after administration of enteric coated tablets of barium sulfate. Worten et al.(19) have compared their radiographic findings with in vitro testing using artificial gastric fluid.

We have used the apparatus described under "Disintegration of Tablets" and shown in Fig. 3 using artificial gastric fluid and neutral intestinal fluid. The formulas for these fluids follow:

Artificial Gastric Fluid (11)

Sodium Chloride	1.400 Gm.
Potassium Chloride	0.500 Gm.
Calcium Chloride	0.060 Gm.
Hydrochloric Acid 36%	6.944 Gm.
Pepsin U. S. P.	3.200 Gm.
Distilled Water	to make 1000.00 cc.

Artificial Intestinal Fluid—Neutral (15)

Pancreatin U. S. P.	2.8 Gm.
Distilled Water	to make 1000.0 cc.

The tablets to be tested are placed on the screen and covered with artificial gastric fluid maintained at 37° C. with slow, constant agitation. After two hours the artificial gastric fluid is replaced by artificial intestinal fluid. Satisfactory enteric coatings should completely protect the tablets against the gastric fluid but they should disintegrate in the intestinal fluid in not less than one hour or more than three hours. This method overcomes the disadvantage of the Maney and Kuever method because the insoluble material washed off the tablets falls through the screen to the bottom of the crystallizing dish leaving the liquid near the surface clear enough to enable one to see the tablets without difficulty. While the methods cited and discussed in this paper are by no means all that are available, they present a cross section and give some idea of the problems involved in the physical control and standardization of compressed and coated tablets in the pharmaceutical manufacturing industry. Although some of the methods leave much to be desired, their use and application assures at least a certain amount of desirable uniformity of the finished product and will often lead to product improvement as well as standardization.

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RECENT OBSERVATIONS ON DENTAL DRUGS: A REVIEW

By A. A. Dodge, Ph. D.*

IT is not intended to attempt to cover exhaustively in this paper the entire field of dental drugs, but rather to review some of the recent reports on the use of penicillin in dentistry, the possibilities of tyrothricin in the same field, clinical observations on the sulfonamides in dental practice, the rôle of sodium fluoride in controlling dental caries, and dental applications of several other drugs.

Penicillin

Until very recently the limitations placed on the distribution of penicillin have made it impossible for the dentist to secure supplies of the drug for clinical trial in civilian practice. Several authors have conjectured upon the probability of the value of penicillin to the dentist.

Smith (1) states that the drug will undoubtedly prove useful in checking staphylococcal or streptococcal infections, especially if the patient fails to respond to sulfonamide therapy. Fechtner (2) considers it likely that penicillin may be indicated in the treatment of facial cellulitis, parotitis, chronic wounds, postoperative infection, unhealed compound fracture, acute abscess, actinomycosis and acute and chronic osteomyelitis.

Cipes (3) advises that if the local application of penicillin fails to produce the desired results, systemic administration should also be employed; in the latter case, cooperation with the patient's physician is indicated. Since it has been demonstrated by Herrell, Heilman and Williams (4) and by Hobby, Meyer and Chaffee (5) that local penicillin therapy has proved successful in the treatment of mastoiditis, blepharitis, chronic conjunctivitis and chronic wound sinuses, together with the knowledge that local application of the drug is effective in

* Assistant Professor in Pharmacy, Philadelphia College of Pharmacy and Science.

destroying staphylococci, streptococci and pneumococci, Cipes feels that it is reasonable to hope for the successful local treatment of such dental disorders as periodontoclasis, osteomyelitis, Vincent's infection, apical granuloma and dry socket infections.

Features of penicillin therapy which make it particularly applicable to dental use are listed by Cipes as follows:

1. Its potency against sulfonamide-resistant bacteria, especially the staphylococcus.
2. Its activity in the presence of serum and pus.
3. Its successful application in treating closed cavities and sinuses, and other reported cases analogous to those found in dental disease.
4. Its action on lactobacilli.
5. Its ability to act when applied topically.

Strock (6) has observed an apparent relationship between the condition of the gingivæ and the administration of penicillin in the treatment of various pathologic conditions, among which were gonorrhea, syphilis, osteomyelitis, septicemia, subacute bacterial endocarditis and brain abscesses.

His observations were made on a group of 198 patients who had received from 80,000 to 9,000,000 units of penicillin. In all of the cases, the gingivæ were remarkable in tone and free from inflammation despite a history in 37 cases of ulceration and spontaneous bleeding at the time penicillin treatment was begun, or a history of bleeding gums for which treatment had been sought within three months prior to penicillin therapy.

Strock was able to study under controlled conditions a group of 15 cases of Vincent's infection for which penicillin therapy was the only treatment used. The patients were not permitted to brush their teeth, use mouth irrigations or employ oral hygienic measures of any kind. No special diets were prescribed, and unlimited smoking was allowed.

Penicillin was administered in various amounts ranging from 1,250,000 units intramuscularly to 5,000 units placed in the mouth and held at rest for lengths of time varying from one hour to continuous bathing, except during eating and sleeping periods.

In all cases there was prompt improvement, giving the impression that penicillin gave impetus to the speed of tissue regeneration and epithelization.

In a second paper Smith (7), in reviewing progress in the pharmacology and therapeutics of penicillin, mentions several cases which are of interest to dentists in connection with the treatment of mandibular infection.

A soldier with a two months' old sinus in the iliac crest was given penicillin, but surgery was eventually found necessary. A sequestrum was found in a cavity lined by fibrous tissue; this suggests that even if apparent sterility is obtained, healing may not occur if fibrosis and avascularity are present.

Several cases of infection which were successfully treated with penicillin included one in which resection of the left side of the mandible from the canine tooth to the temporomandibular joint was performed for an infected multilocular cyst; two bone graft cases; one with a sinus in the mouth; and one in which the right side of the mandible had been resected for odontoma.

Smith concludes that penicillin has a definite potential usefulness in dentistry, though the extent to which it is likely to be used will depend upon how much of the practice of the dentist is surgical in nature. Although the local use of penicillin probably will not yield results as dramatic as those achieved through parenteral administration, it would appear that the drug has a place in the local treatment of infection or in its prevention.

Martin (8) reported in 1944 that encouraging results had been obtained in the treatment of acute ulcerative gingivostomatitis (Vincent's type) through clinical use of pastilles containing penicillin sodium. He recommended that a concentration of 250 or 500 units of the drug per pastille should be employed.

It is highly probable that further clinical trial of such pastilles in dental practice will serve to establish necessary data on the various indications for their use, the optimum strength, and stability on storage.

Tyrothricin

Smith (1) believes that there is a field for investigation in the possible use of tyrothricin, an antibiotic agent consisting of a mixture

of gramicidin and tyrocidin obtained from cultures of *Bacillus brevis,* applied by means of wet packs in the treatment of local infection.

Tyrothricin is not administered parenterally because it causes the lysis of red blood cells and also has its germicidal properties reduced in the blood stream.

Fechtner (2) also feels that this substance may prove to be of interest to the dentist if it can be shown to be effective against organisms present in oral infections. Studies on tyrothricin performed by Johnson (9) and also by Weinstein and Rammelkamp (10) have demonstrated that it is effective *in vitro* against the *Lactobacillus acidophilus,* and it is reported to have shown no toxicity when applied to the oral mucous membranes in the few cases tested.

Sulfonamides

According to Goodall (11) the sulfonamides were first used in dentistry about six years ago. The early observations were principally concerned with the local application of sulfanilamide following extraction. Goodall prefers sulfathiazole to sulfanilamide for local use, however, because it is more widely applicable to the organisms encountered, has a more prolonged effect, and has a favorable phagocytic response. Because it is less soluble than sulfanilamide, it is present in the wound, e. g., a tooth socket, long after the local anesthetic has been eliminated. This is of great importance, since procaine breaks down at least partially into *p*-aminobenzoic acid, which then inhibits the bacteriostatic action of the sulfonamide.

Goodall has found that a sulfathiazole paste in glycerin is a satisfactory mode of applying the drug to the tooth socket after extraction. He emphasizes that only a sterile form of the drug should be used, and that care should be taken not to apply too much of the preparation to the wound, lest it retard healing by causing excessive exudation.

In 1944 Weiner (12) published clinical data on the local use of sulfanilamide and sulfathiazole in extraction wounds. He had previously published a preliminary report (13) based upon 1,065 extractions; and since the present series comprised an additional 1,340 extractions, he felt that definite conclusions might now be drawn.

Of the 1,340 extractions performed in Weiner's second series, 467 served as controls in which no sulfonamide was used. In 433

cases the sockets were packed with sulfathiazole, and in the remaining 440 cases with sulfanilamide.

None of the sockets treated with either of the sulfonamides became infected postoperatively, and only five of the controls, none of which reached the "dry socket" stage.

An inspection of the combined data from both series reveals that infection developed in 10 out of 810 controls, in one out of 814 sockets treated with sulfathiazole, and in none out of 781 treated with sulfanilamide.

Weiner does not advocate the routine use of these sulfonamides as prophylactics against postoperative infection in tooth sockets; instead, he recommends that their use should be based upon the area of operation, the type of extraction, the amount of trauma, the systemic condition of the patient and the degree of infection present before the operation.

The sulfonamides have been found useful in root-canal sterilization. Rosen (14) uses as irrigants either a solution of sulfanilamide in water at 60° C. or a solution of sulfadiazine in 8 per cent triethanolamine. If sulfathiazole is to be used, he applies it either as a powder or as a paste prepared with glycerin. Bacteriologic cultures are employed to determine when the canal may be filled. Rosen has not, however, abandoned the use of eugenol, beechwood creosote, cresatin and triformocreosol, or electrosterilization, in root-canal therapy; he considers these valuable adjuncts to sulfonamide therapy, since the tissues readily tolerate repeated applications of these drugs, and also because some of them are believed to enhance the action of the sulfonamides by assisting in the elimination of the products of protein hydrolysis.

Ross (15) reported in 1944 that he had secured favorable results in 38 cases of root canal therapy through the use of "Azochlorasul," a product containing sulfanilamide, azochloramid and sodium tetradecyl sulfate in triacetin solution. It is believed that the presence of the wetting agent, together with the low surface tension of the solvent, permits the disinfection of all contaminated areas. Ross states that his observations tend to confirm the conclusion reached in 1941 by Neter (16), *viz.*, that sulfanilamide and azochloramid when used together in a suitable dilution, were more effective than four times the concentration of sulfanilamide alone, and twice the concentration of

azochloramid alone, when tested against Group A hemolytic streptococci.

Rosamilia (17) summarized in a comprehensive review published in 1943 the observations of numerous authors on sulfonamide therapy in dentistry. Good results have been obtained in the local treatment of various infections following extraction and in fractures. Opinion is somewhat divided as to the advisability of the routine local use of the sulfonamides in the postextraction socket or the oral administration of these drugs following extraction. Because some patients exhibit a hypersensivity to the sulfonamides, their indiscriminate general use in dentistry is to be discouraged. Where complications due to trauma and infection exist, however, there appears to be a definite indication for sulfonamide therapy.

Sodium Fluoride

Arnold (18) reported in 1943 his studies on the dental caries experience rate of selected 12 to 14-year-old white school children of three Illinois communities.

The cities chosen for the investigation were Aurora, where the water supply has a fluoride content of 1.2 parts per million (p. p. m.) and the dental caries experience rate is low; Oak Park, where the water is fluoride-free, and because of the high economic level there has been an extensive amount of treatment of carious teeth; and Waukegan, where the water is also fluoride-free, and the percentage of treatment is much lower than that of Oak Park.

The incidence of dental caries was found to be markedly less in the case of the Aurora children, i. e., those who had used throughout life a water supply having a fluoride content of the order of 1 p. p. m. This concentration is considerably below the fluoride concentration which produces either the brown stain or the pitting characteristic of moderate and severe fluorosis. Arnold suggests the advisability of adding about 1 p. p. m. of fluoride to all public water supplies which are fluoride-free.

The editor of the *Journal of the American Dental Association* (19) stated in 1944 that there is abundant evidence to warrant the conclusion that dental caries is definitely less prevalent in children who from infancy have used drinking water containing fluoride. A long-term study of this problem, covering one generation from infancy to the

age of fourteen years, has been planned in two cities in New York. In one city the fluoride content of the drinking water would be increased to within the limits of 0.8 to 1.0 p. p. m.; in the other, which would serve as a control, the fluoride content would be less than 0.1 p. p. m.

In 1943 Largent and Moses (20) reported a study made on a human subject to determine the extent to which sodium fluoride might be ingested and absorbed through the direct application of solutions of it to the teeth, a technic which had been suggested by other investigators as a means of increasing the fluoride content.

From the data obtained through the determination of the fluoride content of the urine and feces for a period of time before treatment, during it, and after it, these authors concluded that there is no appreciable systemic absorption of this compound when it is applied according to the technic they described.

Hoyt and Bibby (21) described in 1943 the local use of sodium fluoride as an obtundent for sensitive dentin. A 4 per cent aqueous solution of the chemical produced some degree of desensitization, but much more satisfactory results were secured through the application of a paste consisting of equal parts of sodium fluoride, white clay and glycerin. The effects of this treatment were found to last for many months, varying with the patient.

In 1944 Bibby (22), in considering the rationale and approach to the use of fluorides in the prevention of dental caries, called attention to the observations of Dean, Arnold and Evolve (23) that an inverse relationship between the fluorine content of drinking water and the prevalence of dental caries existed in 21 cities studied. In cities where the water supply contained 1 p. p. m. or more of fluorine, children had only one-third to one-half the caries which existed in other localities where the content was less than 0.5 p. p. m.

In a later paper Bibby (24) published the results of his experiments on a group of children over a period of two years. It was found that six topical applications of a 1:1,000 aqueous solution of sodium fluoride reduced dental caries by more than one-third, compared with the results in untreated quadrants in the same mouth.

Atkins (25) prescribes a mouthwash containing sodium fluoride as a practical means of caries control. He directs that one teaspoonful of a stock solution containing 0.25 mg. of the chemical per cc. be

diluted with half a glass of water and used as a mouthwash immediately after eating.

Observations by Epstein and Schamp (26) indicate that the use of a 1:1,000 solution of sodium fluoride as a mouthwash over a period of six months did not unduly irritate the gingivæ.

Branson (27) advocates the administration of ground bone as more closely following Nature's plan of nutrition, and quotes McClure (27a) as stating that beef bone normally contains more than 350 p. p. m. of fluorine. From 3 to 4 gm. of such bone would provide 1 mg. of fluorine, which is the amount contained in 5 glasses of drinking water having a fluorine content of 1 p. p. m. Of dental interest also is the fact that 4 gm. of bone provide almost as much calcium and phosphorus as are contained in one quart of milk.

Sodium Perborate

In 1944 Glickman and Bibby (28) reported a correlated clinical and histologic study of the effect of repeated applications of sodium perborate upon the gingival mucosa of the dog. Three types of this substance were used: flavored, unflavored, and neutralized ("neutrox").

At the outset of the experiment all of the five animals used had a slight marginal gingivitis with erythema and edema. In no instance was there any evidence that the sodium perborate, applied in the form of a paste, had therapeutic value either in altering this condition or in alleviating the ulcerations or lesions which resulted from its use. On the contrary, healing was actually retarded by continued applications of the paste, and spontaneous healing occurred in all cases when the treatments were discontinued.

The use of either water or a 1 per cent solution of acid calcium phosphate with a pH of 3.1 as an irrigant immediately following treatment produced no appreciable alteration in the effect of sodium perborate on the gingival mucosa.

Thymol

Day (29) has recommended the instillation of melted thymol into carious teeth for the purpose of sterilizing the area.

Through a culturing technic the organisms present in the carious areas were found to be closely related to, if not identical with, *Lacto-*

bacillus acidophilus. The phenol coefficient of thymol against the lactobacillus was determined to be 23.4.

Although there is a limit to the area of decay that can be sterilized by the application of melted thymol, bacteriologic studies of the penetration of the drug indicated a definite sterilization in the presence of large amounts of decay. Through this technic it is possible to leave small areas of decay near the pulp and achieve sterilization without injury to the odontoblastic layer, thus aiding the regeneration of secondary dentin.

The Cationic Wetting Agents

Aqueous solutions of the cationic wetting agents are detergent and have a foaming action. The surface tension, expressed in dynes per sq. cm., of a 1:1000 aqueous solution of several of these is reported by the respective manufacturers as follows: "Ceepryn Chloride" Merrell, 42.0 (at 30° C.); "Phemerol" Parke Davis & Co., 35 (at 25° C.); "Zephiran Chloride" Winthrop, 37.39 (at 25.3° C.).

Solutions of this concentration have been shown to be actively germicidal, although higher dilutions are sometimes used. For use as a swab or spray in the throat, "Phemerol" may be used in a 1:1000 solution; for a mouthwash or gargle, the concentration should be reduced by adding four parts of water or normal saline solution, "Zephiran Chloride" is used in strengths of from 1:1000 to 1:10,000 in the throat.

"Cepacol" Merrell consists of a 1:4000 hydro-alcoholic solution of "Ceepryn Chloride," containing sodium phosphate. It is recommended by its manufacturers as a gargle and throat spray.

For the sterilization of dental instruments, the latter should first be cleaned thoroughly with soap and water and then rinsed well, since the cationic wetting agents are incompatible with soap, which is anionic in character. Immersion for about thirty minutes in a 1:1000 aqueous solution of the cationic wetting agent will sterilize the instruments.

The manufacturers of "Zephiran Chloride" recommend that if dental instruments are to be stored by immersion in a 1:5000 solution of this substance, 1 per cent of sodium nitrite should be added to prevent any corrosion which might otherwise occur over a protracted period. It is claimed that 1:1000 solutions of these agents do not cause the corrosion of instruments on contact lasting for several days.

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SELECTED ABSTRACTS

Epsom Salts and Nutrient Value of Berries. W. L. Powers. *Science 101,* 301 (1945). A definite and profitable response from the application of magnesium to Oregon soils in connection with fertility experiments with cane fruits has been obtained. The application of 30 pounds of magnesium sulfate per acre of Amity silty clay loam resulted in the maximum yield of gooseberries in 1944 and improved cane growth and the appearance of foliage. The net profit was increased $62.25 per acre over the cost of the treatment.

Deficiency of magnesium in the soil produces a leaf blotch similar to leaf scorch from lack of potash. The application of large amounts of potash to correct the latter condition appeared to make any magnesium present in the soil less available to plants. Four plots which were treated with a fertilizer supplying a medium amount of potash yielded a net increase of $10.70 per acre.

Analyses of scorched leaves revealed them to be high in manganese when grown on acid soils with no fertilizer. When available magnesium in such soils is low, liming should precipitate and suppress manganese; magnesium limestone may do this and also supply magnesia which is needed for chlorophyl.

Treatment of a plot of boysenberries with magnesium sulfate to the extent of 40 pounds per acre raised the vitamin C content 24.4 per cent above that of berries grown on an untreated plot. Magnesium sulfate treatment also raised the vitamin C content of raspberries by 4 per cent.

The Compatibility of Chlorocresol With Digitalin and Ergotinine Citrate. G. W. G. Smithers. *Pharm. J. 100,* 164 (1945). Appendix XII of the Second Supplement to the B. P. C. requires that Injection of Digitalin be sterilized by heating with a bactericide, for which purpose either chlorocresol (*p*-chloro-*m*-cresol) or phenylmercuric nitrate is permitted, or by filtration. During three and one-half years' experience with chlorocresol as a bactericide, the author has found that no incompatibility has arisen from its use in preparing injections of epinephrine, amylocaine hydrochloride, apo-

morphine hydrochloride (with 0.05 per cent sodium or potassium metabisulfite), thiamine hydrochloride, atropine sulfate, cotarnine chloride, emetine hydrochloride, homatropine hydrobromide, hyoscine hydrobromide, morphine hydrochloride (also sulfate and tartrate), physostigmine salicylate (in acid solution), and procaine hydrochloride.

Its use, however, in injections of digitalin and of ergotinine citrate caused turbidity. To investigate the incompatibility of chlorocresol with these two substances, solutions of the latter were prepared in a concentration double that usually administered by injection; for digitalin B. P. C. the amount present was 1/5 grain per mil, and for ergotinine citrate 1/50 grain per mil. It may be mentioned that it is customary in England to express the strengths of many parenteral solutions in this combination of the Imperial and metric systems.

Freshly distilled water suitable for injection (pH 6.5 to 7) was used throughout. Each of the two solutions described was divided into four parts and treated as follows:

Part 1. An equal volume of distilled water was added.

Part 2. An equal volume of 0.4 per cent aqueous solution of chlorocresol was added.

Part 3. An equal volume of 0.004 per cent aqueous solution of phenylmercuric nitrate was added.

Part 4. An equal volume of 1 per cent aqueous solution of phenol was added.

The various products were shaken and transferred into 1 mil ampuls; half of these were heated at 100° C. for 30 minutes in a water bath, and the remainder were retained for comparison. The appearance and pH of each solution were noted before and after heating.

The observations are presented in tabular form. Chlorocresol produced turbidity in both the heated and unheated solutions of digitalin and ergotinine citrate, but phenylmercuric nitrate caused no incompatibility in either instance. The use of phenol in the digitalin solutions caused no turbidity, but its use as a bactericide in injections is not officially permitted.

In view of the incompatibility of chlorocresol with digitalin, the same tests were performed on a solution of strophanthin, B. P., since this is also a glycoside. No incompatibility was observed in this case.

The Use of Ionic Exchange Resins for the Purification of Penicillin and Hypertensin. E. Cruz-Coke, F. Gonzalez and W. Hulsen. *Science 101,* 340 (1945). Investigation of the purification of organic substances by filtration through ionic exchange resins revealed that the anionic resin, Ionac A, absorbs proteins, long chain polypeptides, a variety of chromogenic substances and a few amino acids; the cationic resin, Ionac C, retains in addition most amino acids and in particular basic amino acids and amines.

For this process a small funnel with a stem 7 cm. in length and 8 mm. in diameter is filled with 4 gm. of the resin; the latter must be previously washed well with distilled water to remove nitrogen.

The promising results obtained led to trials of the resin for the purification of hypertensin and penicillin.

Hypertensin. This substance is known to lose much of its activity when attempts are made to purify it by use of the usual absorbents. When the crude product was treated with Ionac A, the hypertensive activity was not affected significantly, though chromogens, polypeptides, etc., were removed.

Ionac C was found to absorb the active principle of hypertensin so effectively that elution with a group of 30 substances, including acids, bases, salts, alcohol, other organic solvents, and detergents, failed to release an active eluate.

Penicillin. The crude culture filtrate from *Penicillium notatum* was filtered first through Ionac C at pH 6 to 7, and then through Ionac A at the same pH. The penicillin filtrate thus obtained was found to retain all of the activity of the original material and was free of any toxicity when administered intraperitoneally to mice or intravenously to cats, dogs and man. The penicillin preparation can be concentrated *in vacuo* at low temperatures.

Ointment of Wool Alcohols. J. S. McEwan. *Pharm J. 100,* 166 (1945). The Seventh Addendum to the B. P. allows variations in the proportions of hard, soft and liquid paraffins specified by the Sixth Addendum formula for ointment of wool alcohols. This paper reports the results of trials of various proportions of the paraffins in an attempt to find the most satisfactory ointment for use as such and for the preparation of Unguentum Aquosum.

The anhydrous ointments were prepared by melting the ingredients on a water bath, mixing well, and then allowing them to cool without further stirring. The hydrous ointments were prepared by incorporating warm water into the anhydrous ointment while it was still warm and stirring the mixture until it was cold. All of the ointments thus prepared were smooth and homogeneous immediately after manufacture, but considerable variation was noted on storage at temperatures ranging up to 90° F.

The anhydrous ointment. An increase of the hard paraffin content, with a corresponding decrease in the amount of liquid paraffin, produced harder and more opaque ointments. Those with less hard paraffin and correspondingly more soft paraffin were softer and more translucent. At 90° F. ointments containing either one-half or one-quarter of the nominal hard paraffin content were much too liquid in consistency.

The most satisfactory ointment base for the incorporation of dry ingredients was one containing more soft paraffin and less liquid paraffin than the official preparation. The formula recommended includes wool alcohols 6 per cent, hard paraffin 24 per cent, soft paraffin 30 per cent, and liquid paraffin 40 per cent.

Hydrous ointments. The only preparation which was found capable of resisting separation, especially at 70°–90° F., was one containing 20 per cent of soft paraffin, instead of the 10 per cent specified by the official formula. The increase was made at the expense of the liquid paraffin content.

Sulfathiazole Nasal Jelly in Colds (Further Report). R. S. MacArthur. *Clinical Med. 52,* 92 (1945). Since its introduction 3 per cent sulfathiazole nasal jelly has been used in over 7,000 cases of the common cold without a single complaint of non-effectiveness or unpleasant after-effect. Reports from three pathological laboratories indicate that the preparation is not harmful to the nasal mucosa or cilia. An applicator has been designed to introduce well into the nasal entrance where ciliary activity is most pronounced a measured dose of the jelly containing one-half grain of sulfathiazole.

The observations of several other authors are quoted regarding the effect of pH both upon ciliary activity and the effectiveness of sulfathiazole and sulfadiazine. Ciliary motion is stimulated by an

alkaline medium, but it is decreased at a pH of 6.4 or less. Ordinary water causes a slowing of the ciliary beat when applied to the mucous membrane of the upper respiratory tract. Less intra-nasal discomfort is caused at a pH above 7.4 than by comparable deviations below it. At a pH of 5 or 6 the two sulfonamides mentioned display only a fraction of their maximum activity.

Absorption from the nasal mucosa is stated to be very slow, and it is believed that the hazards of systemic treatment with the sulfonamides are obviated by the local application described.

Untoward Effects of Penicillin: Prophylactic Use in Spina Bifida Operation. S. M. Simon. *Clinical Med. 52,* 87 (1945). Toxic effects were produced by penicillin sodium administered in massive doses to a five-days-old patient who underwent surgery for spina bifida posterior (meningomyelocele). The drug was used as a prophylactic treatment, since the chance of infection and rupture of the sac was great.

Only a few drops of chloroform were sufficient to produce narcosis; this did not produce the cyanosis and apnea noted later in the operation, since the patient was normal for thirty minutes after the anesthesic was discontinued. By means of a needle, about 50 cc. of fluid were aspirated from the sac, immediately after which 100,000 units of penicillin sodium in normal saline solution (5,000 units per cc.) were injected into the subarachnoid space. This was followed within twenty minutes by the injection into the lumbar muscle of an additional 100,000 units of the drug in the same dilution.

Thirty minutes after the second injection, near the close of the operation, the patient became cyanotic. Respiration became irregular, ceasing several times, and convulsion developed. Artificial respiration and the use of oxygen overcame these toxic reactions. It was found necessary to continue the administration of oxygen for three hours, at which time the penicillin level in the blood became depleted and consciousness returned.

Hypersensitivity to the drug cannot be considered to have been present in this case, since an additional 200,000 units of penicillin sodium in divided doses of 25,000 units every eight hours were given intramuscularly following the operation.

Four weeks following the operation the child appeared to be normal in every respect.

SOLID EXTRACTS

The development of a new pocket-size solar still assures a continuous supply of drinking water to aviators forced down in tropical waters. The device consists of a vinyl plastic envelope through the middle of which is stretched a black cellulose sponge. To place it in use, it is inflated like a balloon, tied to the side of the raft, and allowed to float in the sea. The sponge then takes up water and absorbs heat from the sun, whereupon through evaporation and distillation the sea water is converted into drinking water. This solar still now has high priority on the list of equipment used for air-sea rescue work in the Pacific.

AJP

An analysis of typical meals eaten by average Americans has shown that only about 35 per cent receive the minimum daily intake of thiamin, riboflavin, ascorbic acid, calcium and iron. At least 35 per cent of the nutritional value of foods from the standpoint of vitamins is lost in the usual cooking processes.

AJP

The ten most important drugs in 1910 in their order of importance were ether, morphine, digitalis, diphtheria antitoxin, smallpox vaccine, iron, quinine, iodine, alcohol and mercury. In 1945 the list is as follows: antibiotics and sulfonamides; blood and blood fractions; antimalarials; ether and other anesthetics, morphine, cocaine and the barbiturates; digitalis; arsphenamine; immunizing agents, antitoxins and vaccines; insulin and liver extract; other hormones; vitamins.

AJP

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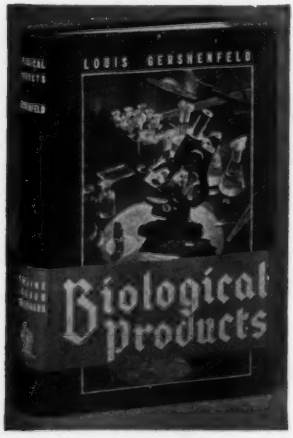

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